Remarks

Reconsideration and withdrawal of the rejections, in view of the remarks and amendments presented herein, is respectfully requested. Claims 20, 21, 24, 29-33, 36-45, 48-53 and 56-65 are currently pending. Claims 20, 24, 29-32, 34-37, 40, 41, 46, 47, 51, 52, and 54-60 are amended. Support for amendment of the claims is found throughout the specification (e.g., page 33, lines 19-21; page 34, lines 5-12; Figure 4; and the original claims). Claims 66 and 67 are cancelled.

The 35 U.S.C. § 112, First Paragraph, Rejection

The Examiner rejected claims 29-31 and 60-67 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that the instant claims encompass yet to be discovered compounds that can alter the nuclear localization and total amount of NR1 in a cell. This rejection is respectfully traversed.

Applicants respectfully submit that tyrosine kinases, tyrosine kinase inhibitors, tyrosine phosphatases, tyrosine phosphatase inhibitors, serine/threonine phosphatases and serine/threonine phosphatase inhibitors are known in the art. Applicants further submit that the experimentation required to make and use the present invention is not undue. Therefore, Applicants respectfully submit that the enablement requirement under 35 U.S.C. § 112, first paragraph, is satisfied and respectfully request reconsideration and withdrawal of the rejections of the claims.

The Examiner rejected claims 29-31 and 60-67 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner

alleges that the instant claims relate to the use of a large genera of compounds that are not supported by a commensurate teaching as to which compounds could actually be used. This rejection is respectfully traversed.

The Examiner notes that the present specification discloses only two polynucleotide sequences, and that this is not sufficient to describe the essentially limitless genera encompassed by the claims. The Examiner is requested to note that the present specification does not disclose any polynucleotide sequences. Thus, the statement that "[t]he nucleic acid itself is required" at page 9 of the Office Action is false.

Applicants respectfully submit that the written description requirement under 35 U.S.C. § 112, first paragraph, is satisfied and respectfully request reconsideration and withdrawal of the rejections of the claims.

The 35 U.S.C. § 102 Rejection

The Examiner rejected claims 20, 21, 29, 32, 33, 36, 37, 42-45, 60 and 61 under 35 U.S.C. § 102 alleging that the claims are anticipated by Rao et al., *Neuron*, 19:801-812 (1997) (Rao herein). This rejection is respectfully traversed.

Rao teaches the application of APV (an NMDA receptor antagonist), CNQX (an antagonist of the AMPA-type glutamate receptor), or nifedipine (an L-type voltage-dependent calcium channel antagonist) to cells to prevent activation of the NMDA receptor (page 802, left column; page 804, left and right columns). Rao found that chronic activity blockade of hippocampal cultures with the NMDA receptor antagonist 2-amino-5-phosphonovalerate (APV) changes the subcellular distribution of the NMDA receptor with no effect on the AMPA-type glutamate receptor (abstract; page 801, right column). Activity blockade induced an increase both in the total number of NMDA receptor clusters (hot spots) and in their targeting to synaptic sites (page 801, right column). However, there was not a generalized increase in the amount of NR1 at all sites but indeed a shift in the distribution (page 802, right column). Western blot analysis showed no change in the amount of NR1 in the APV-treated compared to control

cultures (page 803, left column). Rao incubated 3 week APV-treated neurons (with synaptic NMDA receptor clusters) for a fourth week in the absence of APV, thus allowing the cells to return to their normal levels of spontaneous activity (page 803, right column to page 804, left column). The resumption of spontaneous activity resulted in a large decrease in synaptic NR1 clusters compared to the 3- or 4-week APV-treated neurons (page 804, left column). The only instance when Rao discloses use of an NMDA activator is when Rao reports that addition of 5 μM NMDA largely blocked the increase in NR1 cluster number and shift to synaptic sites induced by TTX (tetrodotoxin) (page 804, left column).

Claim 20 is directed to a method for identifying a compound that alters NR1 subunit distribution in a cell, the method comprising: contacting a test cell with a compound; activating an NMDA glutamate receptor present on the test cell and on a control cell; and detecting the distribution of NR1 subunit in the test cell and in the control cell, wherein an alteration in the distribution of NR1 subunit in the test cell contacted with the compound relative to the distribution of NR1 subunit in the control cell not contacted with the compound indicates the compound alters the distribution of NR1 subunit in the test cell.

Claim 29 is directed to a method for altering NR1 subunit distribution in a cell, the method comprising: contacting a test cell with a compound selected from the group consisting of a tyrosine kinase, a tyrosine kinase inhibitor, a tyrosine phosphatase, a tyrosine phosphatase inhibitor, a serine/threonine phosphatase, or a serine/threonine phosphatase inhibitor; activating an NMDA glutamate receptor present on the test cell and on a control cell; and detecting the distribution of NR1 subunit in the test cell and the control cell, wherein the distribution of NR1 subunit in the test cell contacted with the compound is altered relative to the distribution of NR1 subunit in the control cell not contacted with the compound.

With regard to claim 20, Rao does not teach a method comprising .... activating an NMDA glutamate receptor present on the test cell and on a control cell ... wherein an alteration in the distribution of the NR1 subunit in the test cell contacted with the compound relative to the

distribution of NR1 subunit in the control cell not contacted with the compound indicates that the compound alters the distribution of NR1 subunit in the cell.

With regard to claim 29, Rao does not teach a method comprising .... activating an NMDA glutamate receptor present on the test cell and on a control cell .... wherein the distribution of NR1 subunit in the test cell contacted with the compound is altered relative to the distribution of NR1 subunit in the control cell not contacted with the compound.

The only instance when Rao teaches activation of an NMDA receptor present on a cell is when NMDA was used in combination with tetrodotoxin (TTX) (Figure 3 and page 804, left column). Rao teaches contacting a cell with a compound (TTX) and contacting a cell with a compound (TTX) in combination with an NMDA glutamate receptor activator (NMDA) (Figure 3 and page 804). Rao does not disclose activating an NMDA glutamate receptor present on a control cell in the absence of an additional compound.

Accordingly, Rao fails to teach every element of claims 20 and 29.

With regard to Claim 21, Rao does not teach a method that involves activating an NMDA glutamate receptor present on the cell; and detecting the amount of NR1 subunit in the cell. Rather, Rao is completely silent with regard to whether addition of 5 μM NMDA to TTX treated cultures (cells) affected the amount of NR1 subunit in the cells. Accordingly, Rao does not teach every element of claim 21.

Applicants respectfully submit that Rao does not teach all of the elements of the claims. Accordingly, the Examiner is respectfully requested to withdraw the rejections of the claims under 35 U.S.C. § 102.

The 35 U.S.C. § 103 Rejections

The Examiner rejected claims 24, 38, 39, 48, 49, 52, 53, 56, 57, 66, and 67 under 35 U.S.C. § 103 alleging that the claims are unpatentable over Rao et al., *Neuron*, 19:801-812 (1997) in view of Wang et al., *PNAS*, 93:1721-1725 (1996) (Wang herein). This rejection is respectfully traversed.

Rao speculates that phosphorylation may be a potential mechanism for the APV-induced redistribution of NMDA receptors and that other phosphorylation events modifying NR2 or PSD-95 or novel anchoring proteins may be regulatory (page 805, right column; page 808, right column). APV is an NMDA receptor antagonist.

Wang discloses that a peptide inhibitor of protein tyrosine kinase applied intracellularly caused a decrease in NMDA currents even when ATP was included (abstract). This assay was conducted under conditions in which blockade of NMDA channels was removed (page 1721, right column).

Claim 24 is directed to a method for identifying a tyrosine kinase inhibitor that alters NR1 subunit distribution in a cell, the method comprising: contacting a test cell with a tyrosine kinase inhibitor; activating an NMDA glutamate receptor present in the test cell and in a control cell; and detecting the distribution of NR1 subunit in the test cell and in the control cell, wherein an alteration in the distribution of NR1 subunit in the test cell contacted with the tyrosine kinase inhibitor relative to the distribution of NR1 subunit in the control cell not contacted with the tyrosine kinase inhibitor indicates the tyrosine kinase inhibitor alters distribution of NR1 subunit.

The Examiner asserts that one of ordinary skill would be motivated to assay tyrosine kinase inhibitors and tyrosine phosphatase inhibitors as taught by Wang in the method of Rao, alleging that the motivation to do so is provided by Rao who teach that activity regulates the subcellular distribution of NMDA receptors and by Wang who teach that tyrosine phosphorylation modulates activity (page 4 of Office Action mailed 18 May 2004). Applicants emphasize that Rao speculated that phosphorylation may be a potential molecular mechanism through which redistribution of NMDA receptors resulting from chronic blockade of NMDA receptors with APV occurs (page 805, right column; abstract). Rao does not teach or suggest that phosphorylation alone will cause redistribution of NMDA receptors.

Applicants additionally submit that the Examiner has failed to factually support a *prima facie* conclusion of obviousness. The combination of Rao and Wang, alone or in combination, fails to teach a method comprising contacting a test cell with a tyrosine kinase inhibitor;

activating an NMDA glutamate receptor present in the test cell and in a control cell .... wherein an alteration in the distribution of NR1 subunit in the test cell contacted with the tyrosine kinase inhibitor relative to the distribution of NR1 subunit in the control cell not contacted with the tyrosine kinase inhibitor indicates the tyrosine kinase inhibitor alters distribution of NR1 subunit.

As described above, Rao fails to disclose activating an NMDA glutamate receptor present on a control cell in the absence of an additional compound (such as a tyrosine kinase inhibitor) and Wang is completely silent with regard to such a method. Accordingly, the cited documents do not teach or suggest all of the claim limitations.

Applicants also submit that Rao speculates that phosphorylation may provide a mechanism through which APV-induced (chronic NMDA receptor blockade) redistribution of NMDA receptors occurs. In contrast, Wang teaches a method wherein NMDA blockage is specifically removed thereby teaching away from the method of Rao. Accordingly, combining the method of Rao with that of Wang would cause both methods to fail. Therefore, Applicants submit that there is no suggestion or motivation to combine the method of Rao with that of Wang and that there is no reasonable expectation of success in making such a combination.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 103.

The Examiner rejected claims 38-41, 48-51, 58, 59, 64, 66 and 67 under 35 U.S.C. § 103 alleging that the claims are unpatentable over Rao et al., *Neuron*, 19:801-812 (1997) in view of Ehlers et al., *Science*, 269:1734-1737 (1995) (Ehlers herein). This rejection is respectfully traversed.

Ehlers teaches that TPA (protein kinase C activating 12-O-tetradecanoyl phorbol-13-acetate) treatment of NR1A-expressing QT6 cells (quail fibroblasts) induced the rapid redistribution of NR1A protein from discrete, concentrated stretches associated with the plasma membrane to interior regions of the cell (page 1736, center column). Thus, while Ehlers expressed an NR1A subunit, Ehlers did not express a functional NMDA receptor in a cell.

Ehlers is completely silent with regard to the activation of any NMDA receptor. Ehlers is also silent with regard to any method that includes the comparison of a test cell to a control cell or determination of the amount of NR1 subunit in a cell.

Applicants submit that the Examiner has failed to factually support a *prima facie* conclusion of obviousness. For example, Applicants respectfully submit that the combination of Rao and Ehlers fails to teach or suggest all of the limitations of the claims.

With regard to claim 21, Rao and Ehlers, alone or in combination, fail to teach a method for identifying a compound that alters the amount of NR1 subunit in a cell, the method comprising: contacting a cell with a compound; activating an NMDA glutamate receptor present on the cell; and detecting the amount of NR1 subunit in the cell; wherein an alteration in the amount of NR1 subunit in the cell contacted with the compound relative to the amount of NR1 subunit in a cell not contacted with the compound indicates the compound alters the amount of NR1 subunit in the cell. Rather, both Rao and Ehlers are completely silent with regard to a method that includes detecting the amount of NR1 subunit in a cell.

With regard to claim 20, Rao and Ehlers, alone or in combination, fail to teach a method for identifying a compound that alters NR1 subunit distribution in a cell, the method comprising: contacting a test cell with a compound; activating an NMDA glutamate receptor present on the test cell and on a control cell; and detecting the distribution of NR1 subunit in the test cell and in the control cell, wherein an alteration in the distribution of NR1 subunit in the test cell contacted with the compound relative to the distribution of NR1 subunit in the control cell not contacted with the compound indicates the compound alters the distribution of NR1 subunit in the cell.

With regard to claim 24, Rao and Ehlers, alone or in combination, fail to teach a method for identifying a tyrosine kinase inhibitor that alters NR1 subunit distribution in a cell, the method comprising: contacting a test cell with a tyrosine kinase inhibitor; activating an NMDA glutamate receptor present in the test cell and in a control cell; and detecting the distribution of NR1 subunit in the test cell and in the control cell, wherein an alteration in the distribution of NR1 subunit in the test cell contacted with the tyrosine kinase inhibitor relative to the

distribution of NR1 subunit in the control cell not contacted with the tyrosine kinase inhibitor indicates the tyrosine kinase inhibitor alters distribution of NR1 subunit.

With regard to claim 29, Rao and Ehlers, alone or in combination, fail to teach a method for altering NR1 subunit distribution in a cell, the method comprising: contacting a test cell with a compound selected from the group consisting of a tyrosine kinase, a tyrosine kinase inhibitor, a tyrosine phosphatase, a tyrosine phosphatase inhibitor, a serine/threonine phosphatase, or a serine/threonine phosphatase inhibitor; activating an NMDA glutamate receptor present on the test cell and on a control cell; and detecting the distribution of NR1 subunit in the test cell and the control cell, wherein the distribution of NR1 subunit in the test cell contacted with the compound is altered relative to the distribution of NR1 subunit in the control cell not contacted with the compound.

With regard to claims 20, 24 and 29, Rao and Ehlers, alone or in combination, fail to teach or suggest any method that includes activating an NMDA glutamate receptor present in a test cell and in a control cell; and detecting the distribution of NR1 subunit in the test cell and in the control cell. Accordingly, Rao and Ehlers fail to teach or suggest all of the claim limitations.

Applicants respectfully submit that there is no motivation to combine the teachings of Rao with those of Ehlers. Rao investigated the effect of receptor activity on the subcellular distribution of NMDA receptors in hippocampal neurons in culture (abstract).

Ehlers investigated the molecular mechanisms underlying the localization of NMDA receptors by expressing the NR1 subunit of the NMDA receptor in QT6 quail fibroblasts (abstract). Immunoblot analysis of QT6 cell lysates showed that QT6 cells do not express endogenous forms of the GluR1, NR1, and GluR6 receptor subunits. Staining for an NMDA subunit was specific for cells that were transfected with a cDNA encoding the subunit (page 1735, left column). Thus, use of the QT6 cells allowed Ehlers to detect the position of the NR1 subunit due to the lack of interfering NMDA subunits.

Applicants respectfully submit that one of skill in the art would not be motivated to combine the teachings of Rao with those of Ehlers because, for example, Rao utilizes neurons

that express an intact NMDA receptor and Ehlers utilizes fibroblasts that express a transfected NR1 NMDA receptor subunit. Furthermore, the neurons used by Rao endogenously express numerous NMDA receptor subunits while the QT6 quail fibroblasts used by Ehlers do not endogenously express the GluR1, NR1 or GluR6 NMDA receptor subunits. Thus, combining the teachings of Rao with those of Ehlers would defeat the method of Rao because, for example, it would involve utilizing an NMDA receptor subunit instead of an NMDA receptor. Combining the teachings of Ehlers with those of Rao would defeat the method of Ehlers because, for example, Ehlers would express an NMDA receptor subunit in a neuron that expresses numerous NMDA receptor subunits which would defeat the detection method of Ehlers through interference.

Applicants emphasize that there is no reasonable expectation of success upon combining the teachings of Rao with those of Ehlers because to do so would cause both methods to fail.

Applicants respectfully submit that the combination of Rao and Ehlers does not render obvious claims 20, 21, 24 and 29, or claims that depend therefrom. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 103.

Allowable Subject Matter

The Examiner indicated that claims 34, 35, 46, 47, 54 and 55 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims.

Applicants respectfully submit that claims 34, 35, 46, 47, 54 and 55 were amended in accordance with the instructions received from the Examiner. Therefore, allowance of the claims is respectfully requested.

Summary

It is respectfully submitted that the pending claims 20, 21, 24, 29-33, 36-45, 48-53 and 56-65 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 17 day of August, 2004, at 8:05 (Central Time).

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